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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/089,583	PLESTED ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/14/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48,49,55,56 and 62-81* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,49,55,56 and 62-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 112406.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Page 2 of 9/13/02 IDS*.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 11/24/06 has been entered.

Applicants' Amendments

2) Acknowledgment is made of Applicants' amendment filed 11/24/06 and 03/14/07 in response to the final Office Action mailed 11/02/05. The latter is compliant with 37 C.F.R 1.121.

Status of Claims

3) Claims 48 and 55 have been amended via the amendment filed 03/14/07.

New claims 62-81 have been added via the amendment filed 03/14/07.

Claims 48, 49, 55, 56 and 62-81 are pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Information Disclosure Statement

6) Acknowledgment is made of Applicants' Information Disclosure Statement filed 09/05/06. The information referred to therein has been considered, except for the documents, which have already been considered or cited on a PTO-892 or a previously considered IDS, and a signed copy is attached to this Office Action.

Rejection(s) Withdrawn

7) The rejection of claims 48, 49, 55 and 56 made in paragraph 11 of the Office Action mailed 11/02/05 and maintained in paragraph 16 of the Office Action mailed 03/14/06 under 35 U.S.C §

112, first paragraph, as containing new subject matter, is withdrawn.

8) The rejection of claims 48, 49, 55 and 56 made in paragraph 13 of the Office Action mailed 11/02/05 and maintained in paragraph 17 of the Office Action mailed 03/14/06 under 35 U.S.C § 102(b) as being anticipated by Plested *et al.* (*Infect. Immun.* 67: 5417-5426, October 1999, already of record), is withdrawn in light of Applicants' amendment withdrawn.

Rejection(s) under 35 U.S.C § 112, First Paragraph (Scope of Enablement)

9) Claims 48, 49, 55, 56 and 62-81 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of immunizing a subject against *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12 comprising administering to said subject an immunogenic composition comprising a conserved inner core of a neisserial lipopolysaccharide (LPS) that lacks outer core of said LPS, wherein a phosphatidylethanolamine moiety is linked to position 3 of HepII moiety of said inner core and wherein the method induces an antibody that binds to LPS inner cores of L1, L3, L7, L8, L9, L10, L11 and L12 immunotypes of *Neisseria meningitidis* and that has specific opsonic activity against a *galE* mutant of immunotype L3 *Neisseria meningitidis* and a wild type immunotype L3 *Neisseria meningitidis,* does not reasonably provide enablement for a method of eliciting in a host an antibody as claimed in claims 48 and 62-65, a method of immunizing a host as claimed in claims 55 and 66-69, a method for eliciting in a host an antibody as claimed in claims 70 and 72-75, a method of immunizing a host as claimed in claims 76 and 78-81, wherein the method comprises administering to said host an immunogenic composition that 'comprises' an outer core-containing inner core of a *Neisseria* LPS and elicits an antibody that binds to inner core LPS of L1, L3, L7, L8, L9, L10, L11 and L12 immunotypes of *Neisseria meningitidis* or that binds to inner core LPS of a majority of naturally occurring *Neisseria meningitidis* strains; and is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain, as claimed broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400

(Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention pertains to a method of immunizing a host against *Neisseria meningitidis* immunotypes L1, L3 and L7 to L12, or a method of eliciting an antibody in a host that recognizes *Neisseria meningitidis* immunotypes L1, L3 and L7 to L12 or binds to an inner core LPS of a majority of naturally occurring strains of *Neisseria meningitidis* comprising administering an immunogenic composition comprising an inner core of a *Neisseria* LPS wherein a phosphoethanolamine moiety is linked to position 3 of a HepII moiety of said inner core of said *Neisseria* LPS, wherein an antibody is elicited that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3 and L7 to L12; and is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis*. Because of the open claim language 'comprising', the immunogenic composition recited in the independent claims 48, 55, 70 and 76, and the dependent claims 62-69, 72-75 and 78-81, is not required to lack an outer core of said neisserial LPS, but is permitted to contain said outer core. In other words, the immunogenic composition recited in these claims, while containing the outer core LPS with said inner core LPS, elicits an antibody of said binding and functional activities. The limitation 'inner core of a *Neisseria* lipopolysaccharide' is not limited to a *galE* inner core of a neisserial LPS that intrinsically lacks outer core LPS, but encompasses a non-*galE* inner core of a neisserial LPS comprising the LPS outer core therein, in an isolated or non-isolated form, or conjugated or non-conjugated form. Because 'an inner core of a *Neisseria* LPS' present in the composition recited in claims 48, 55, 70 and 76 is not required to lack an outer core of said LPS, the method claimed in these claims is required to elicit an antibody in any generic host wherein the antibody: (i) binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12; and (ii) is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain, upon administration to said host an immunogenic

composition that comprises an inner core of any *Neisseria* LPS having the intact outer core wherein the phosphoethanolamine moiety is linked to position 3 of HepII moiety of said inner core. However, the instant specification is not enabling for such methods as claimed wherein the administration of an immunogenic composition comprises an outer core-containing inner core of a neisserial LPS having a phosphoethanalamine moiety linked to position 3 of HepII moiety of said neisserial inner core elicitssaid antibody. The only *Neisseria* LPS inner core species having a phosphoethanolamine moiety linked to position 3 of HepII moiety of the inner core that has been used in the administered immunogenic composition of the instant specification is the *galE Neisseria meningitidis* immunotype L3 LPS inner core lacking the outer core. An outer core-containing inner core neisserial LPS of the recited structure is not shown within the instant specification to induce an antibody in a host that has the recited binding activity and the recited passive protective capacity. This is important because the third paragraph on page 4 of the instant specification states the following:

> ..... given the presence of the outer core LPS structure and other surface exposed non-LPS structures, including capsule, it is not known whether the inner core structure is accessible to the immune system to allow a bactericidal immune response to be generated.

With this, it is apparent that at the time of filing of the instant invention, it was neither known nor predictable in the art whether an outer core-containing and/or surface antigens-containing neisseria LPS inner core was accessible to a host's immune system and was capable of elciting an antibody that is bactericidal, let alone an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3 and L7 to L12; that recognizes or binds an inner core LPS of a majority of naturally occurring strains of *Neisseria meningitidis;* and/or is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain, as recited in the instant claims.

Furthermore, the limitation 'host' in the base claims encompasses a mammalian and a non-mammalian host, a human host including a human child, or a non-human host such as an infant rat. The phrase in the base claims 'antibody ... capable of conferring passive protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain' in the base claims leaves open the specific host(s) in whom the antibody is capable of conferring passive protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain. The conferring of passive

protection against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis* strain does not exclude but includes passive protection being conferred to a human host or an infant rat host against a *galE* mutant of an L3 immunotype of *Neisseria meningitidis.* The need for passive protection against any immunotype or strain of *Neisseria meningitidis* in a given host exists only if said immunotype or strain is virulent or pathogenic. The state of the art at the time of the instant invention documented that *galE* mutation dramatically alters the virulence potential of meningococci and that *galE* mutants of *Neisseria meningitidis* are "both serum sensitive and **avirulent** for infant rats", the avirulence being independent of encapsulation. See the first full sentence in left column on page 164 and the first two full sentences under 'Discussion' of Vogel *et al.* (*Microbiol. Immunol.* 186: 159-166, 1997) (Vogel *et al.*, 1997). Vogel *et al.* (1997) further discussed a previous study by Vogel *et al. Med. Microbiol. Immunol.* 185: 81-87, 1996 (Vogel *et al.*, 1996) on the meningococcal virulence in the infant rat model, which demonstrated that only the wild-type strains exhibited the capacity to spread systemically. See left column on page 160 of Vogel *et al.* (1997). The *galE* mutant of *Neisseria meningitidis* lacking the terminal three sugars of the LPS was shown to be avirulent despite the presence of a capsule, and was shown not to spread systemically into the blood stream even in animals infected with 10^8 CFU. No *galE Neisseria meningitidis* could be reisolated from the blood of even those animals that received a challenge dose of 10^8 CFU of *galE Neisseria meningitidis.* See paragraph bridging pages 85 and 86; paragraph bridging left and right columns on page 83; and right column of page 83; and Figure 1 of Vogel *et al.* (1996). The only hosts in which the only antibody, i.e., the monoclonal B5 antibody, that is evaluated in the instant specification for its ability to confer the supposed 'passive protection' against *galE* mutant of an L3 immunotype of *Neisseria meningitidis,* are infant rats. It should be noted that the challenge innoculum of the *galE* mutant of *Neisseria meningitidis* that Applicants used in their infant rat model is also 1 x 10^8 CFU (see the paragraph bridging pages 53 and 54 and the paragraph bridging pages 57 and 58 of the instant specification), a dose that is identical to the dose of 10^8 CFU of *galE Neisseria meningitidis* that is shown by Vogel *et al.* (1996) not to disseminate systemically in the infant rat model. Therefore, at least in infant rat hosts, the recited antibody cannot be charactized as having 'passive protective capacity' against *galE* mutant of an L3 immunotype of *Neisseria meningitidis.* An animal model of passive protection that uses an avirulent *Neisseria meningitidis* as the challenging or infecting strain is of

little prophylactic significance in said animals. Furthermore, how this passive protection in an avirulent infant rat animal model relates to or correlates with passive protection in a human adult or infant host against homologous *galE* mutant of an L3 immunotype of *Neisseria meningitidis*, or a heterologous virulent, invasive, wild typeL3 immunotype of *Neisseria meningitidis,* is neither disclosed nor known. The rate of occurrence of *galE* mutants among naturally occurring carrier or clinical isolates of L3 immunotype *Neisseria meningitidis* is not known or disclosed.

The method claimed in new claims 64, 68, 74 and 80 used an immunogenic composition comprising an inner core of a *Neisseria* LPS of the recited structure being conjugated to a protein or peptide. However, a method of eliciting an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain comprising administering a formalin-killed, *outer core-lacking galE* mutant whole cells of *Neisseria meningitidis* H44/76 strain does not enable a method of eliciting an antibody that binds to an inner core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, and is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain comprising administering an immunogenic composition comprising an inner core of any *Neisseria* LPS wherein said inner core, with or without the intact outer core, is conjugated to a protein or peptide. The process of conjugation to a protein or peptide can block the conserved inner core epitope or the protective inner core epitope, can alter the conformational integrity of the inner core, and/or can modify the chemical structure of the inner core regardless of whether the inner core lacks or has the outer core. With regard to the immunogenicity of inner core LPS conjugates and their ability to induce functional antibodies, page 35 of the instant specification states the following [Emphasis added]:

> **Future studies will look at** the safety and immunogenicity of inner core LPS-conjugates (PEtn at 3-position of HepII and alternative glycoforms) and the functional ability of the polyclonal antibodies in opsonic and serum bacterial assays, initially in mice and rabbits.

For all the reasons explained above, instant claims are viewed as being non-enabled with respect to their full scope. Due to the lack of specific disclosure and/or guidance, the breadth of the instant claims, the lack of working examples enabling the full scope of the claims, the art-recognized avirulence of *galE Neisseria meningitidis*, the art-recognized unpredictability

associated with the immunogenicity of an inner core composition that comprises LPS outer core and other surface antigens, and the quantity of experimentation necessary, a considerable amount of undue experimentation would have been required at the time of the effective filing date of the instant application for one of skill in the art to reproducibly practice the claimed invention. The instant claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

10) Claims 48, 49, 55, 56 and 62-81 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 48 and 55, as amended, and new claims 70 and 76, are vague, indefinite and confusing in the limitations: 'position 3 of a HepII moiety of said inner core' and 'an inner core LPS'. Does it mean that said LPS of *Neisseria meningitidis* has or can have more than one inner core and said inner core has or can have more than one HepII moieties?

(b) Claims 48, 55, 70 and 76 are vague, indefinite, and inconsistent in the limitations: 'an inner core of a ..... lipopolysaccharide' and 'an inner core LPS', because it is unclear how one differs from the other in terms of scope.

(c) Claim 48 is indefinite, confusing and inconsistent in scope in the limitations: 'an antibody ... recognizes *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12' (see lines 1-4) and 'said antibody binds to an inner core LPS of immunotypes L1, L3, L7, L8, L9, L10, L11 and L12'. While the latter phrase requires the antibody to bind to an inner core LPS of immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, the former phrase is broader in scope which does not require the antibody to bind to an inner core LPS of immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, but to recognize *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12, which recognition can occur via binding to a non-inner core epitope within the LPS of said *Neisseria meningitidis* immunotypes. For the purpose of distinctly claiming the subject matter, it is suggested that Applicants replace the phrase 'an antibody ... recognizes *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11 and L12,' in lines 1-4 of the claim with the phrase --an antibody that binds specifically to inner core of lipopolysaccharide of

Neisseria meningitidis immunotypes L1, L3, L7, L8, L9, L10, L11 and L12- and delete the phrase from lines 7 and 8 of the claim: 'binds to an inncer core LPS of *Neisseria meningitidis* immunotypes L1, L3, L7, L8, L9, L10, L11, and L12; and'.

(d) Claims 62, 66, 71 and 78 are vague and indefinite in the limitation: 'in a presence of an outer core LPS', because it is unclear what is encompassed in this limitation. Is this 'an outer core' of said *Neisseria* LPS, an outer core LPS of a meningococcus, an outer core LPS of a gonococcus, an outer core LPS of *Shigella*, or *Francisella* ? Furthermore, does the limitation 'an outer core LPS' mean that said LPS has or can have more than one outer core?

(e) Claims 64, 67, 72 and 79 are vague and indefinite in the limitation: 'in a presence of a bacterial capsule', because it is unclear what is encompassed in this limitation. Is this 'a bacterial capsule' of said *Neisseria meningitidis* strain, a capsule of a non-*Neisseria*, a capsule of *Haemophilus* sps., or a capsule of a fungus? Furthermore, does the limitation 'a bacterial capsule' mean that said has *Neisseria meningitidis* or can have more than one outer core?

(f) Claims 64, 65, 68, 69, 74, 75, 80 and 81 are indefinite because these claims appear to lack proper antecedent basis in the limitation: 'said inner core of a *Neisseria* LPS'. These claims depend from claim 48, 55, 70, or 76, which already recites 'a *Neisseria* lipopolysaccharide (LPS)'. Does it mean that the 'a *Neisseria* LPS' recited in the dependent claims 64, 65, 68, 69, 74, 75, 80 and 81 is different from the one recited in the base claim?

(g) Claims 48, 55, 70 and 76 are indefinite in the limitation: 'capable of conferring passive protection against a galE mutant of an L3 immuntype *Neisseria meningitidis* strain' because it is unclear in whom the recited antibody is capable of conferring passive protection against a *galE* mutant of an L3 immunotype *Neisseria meningitidis* strain. This is important because the state of the art recognizes that *galE* mutation dramatically alters the virulence potential of meningococci and that *galE* mutants of *Neisseria meningitidis* are "both serum sensitive and **avirulent** for infant rats", the avirulence being independent of encapsulation. See the first full sentence in left column on page 164 and the first two full sentences under 'Discussion' of Vogel *et al.* (*Microbiol. Immunol.* 186: 159-166, 1997) (Vogel *et al.*, 1997). Therefore, the limitation identified above is vague and appears to be repugnant because the art recognizes *galE* mutant of *Neisseria meningitidis* to be an avirulent or non-pathogenic strain that does not require or necessitate passive protection.

(h) Claims 49 and 62-65, which depends from claim 48; claims 56 and 66-69, which depend from claim 55; claims 71-75, which depend from claim 70; and claims 77-81, which depend from claim 76, are also rejected as being indefinite because of the indefiniteness identified in the base claims.

Rejection(s) under 35 U.S.C § 102

11) Claims 48, 49, 55, 56 and 62-81 are rejected under 35 U.S.C § 102(b) as being anticipated by van der Ley *et al.* (*Mol. Microbiol.* 19: 1117-1125, 1996, already of record) as evidenced by Poolman JT (*Infectious Agent and Disease* 4: 13-28, 1995) and Vogel *et al.* (*Microbiol. Immunol.* 186: 159-166, October 1997) or van der Ley *et al.* (*Vaccine* 13: 401-407, 1995) (van der Ley *et al.*, 1995).

It is noted that the instant specification identifies H44/76 strain of *Neisseria meningitidis* as an L3 immunotype strain. The specification on page 6 states that *galE* mutant lack outer core structures. See the Table on page 36, and first paragraph on page 47 of the instant specification. It is further noted that the inner core of a *Neisseria* LPS comprised in the recited immunogenic composition is not required to be from a *galE Neisseria* mutant, and therefore the outer core is not excluded, but is included in the recited composition comprising an inner core of a *Neisseria* LPS.

van der Ley *et al.* taught a method of immunizing experimental animals by administering immunogenic meningococcal *galE* mutant LPS that elicited antibodies recognizing novel epitopes in the inner-core region. One of the antibodies thus elicited binds to the *galE* mutant *and* wild-type strains. van der Ley *et al.* also taught a method of immunizing experimental host animals with an outer membrane complex preparation from a *galE* mutant of strain H44/76 (L3 immunotype) of *Neisseria meningitidis* mixed in an adjuvant, and the selection of positive hybridomas using *galE* LPS as the coating antigen in ELISA. See paragraph bridging pages 1122 and 1123; and last full paragraph on page 1123. The prior art LPS-containing immunogen administered to experimental animals is derived from the *galE* mutant of the same identical H44/76 strain of *Neisseria meningitidis* that is used by Applicants to generate MAb B5 specific to the neisserial inner core LPS. Since the prior art immunogenic inner core-containing *galE* mutant LPS or the prior art inner core-containing outer membrane complex preparation from the *galE* mutant of strain H44/76 of *Neisseria meningitidis* are not fully purified, they are expected to

comprise a contaminant protein or pepetide naturally conjugated thereto. That the prior art LPS-containing immunogen derived from the *galE* mutant of the same identical H44/76 strain of *Neisseria meningitidis* as that used by Applicants comprises a phosphoethanolamine moiety linked to position 3 of HepII moiety is inherent from the teachings of van der Ley *et al.* in light of what is well known in the art. For instance, Poolman JT disclosed of the existence of phosphoethanolamine moiety linked to position 3 of Hep2 moiety of the inner core of the lipopolysaccharide of native and *galE* immunotype L3 of *Neisseria meningitidis.* See Figure 2. That the prior art LPS-containing immunogen derived from the *galE* mutant of lacks an outer core in the LPS is also inherent from the teachings of the prior art in light of what is known in the art. For instance, Vogel *et al.* showed that *galE* mutation results in a truncated LPS that lacks the outer core (see Figure 1). Similarly, van der Ley *et al.* (1995) taught that *galE* deletion in *Neisseria meningitidis* leads to the synthesis of galactose-deficient LPS in addition to teaching the desirability of lack of lack of lacto-N-neotetraose structure in a *galE* vaccine strain (see paragraph bridging page 403). Therefore, the prior art method necessarily elicits an antibody that has the intrinsic ability to recognize *Neisseria meningitidis* immunotypes L1, L3 and L7-L12 in the presence or absence of an outer core LPS, and the intrinsic capability of conferring passive protection against a *galE* mutant of an *Neisseria meningitidis* L3 immunotype strain. The accessibility to the recited antibody in the presence of a bacterial capsule is not a property of the recited antibody, but is an intrinsic property of the inner core LPS of the recited immunotypes or naturally occurring strains of *Neisseria meningitidis.* The prior art method, which elicits antibodies both to the *galE* mutant *and* wild-type strains of *Neisseria meningitidis* is expected to necessarily immunize the murine host against 'a majority' of naturally occurring strains of *Neisseria meningitidis* in light of what was known in the art at the time of the invention. For instance, Poolman taught that L3 immunotypes alone account about 80% of (i.e., majority of) meningococcal isolates from group B cases. See Figure 3 of Poolman.

The Office's position that van der Ley's method is the same as the Applicants' method is based upon the fact that the prior art method uses the inner core-containing immunogen composition from the same L3 immunotype H44/76 strain of *N. meningitidis* as the one used by Applicants in the instant specification. Therefore, the prior art inner core-containing immunogen is expected to necessarily have the same intrinsic structure and the same immunogenic, protective,

and/or cross-reactive properties as that of the Applicants' immunogenic composition. Since the Office does not have the facilities for examining and comparing Applicants' method with that of the prior art method, the burden is on Applicants to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the prior art method does not induce the same functional effects as the claimed method). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald et al.*, 205 USPQ 594.

Claims 48, 49, 55, 56 and 62-81 are anticipated by van der Ley *et al.* The reference of Poolman, Vogel *et al.* (1997) or van der Ley *et al.* (1995) is **not** used as a secondary reference in combination with van der Ley *et al.*, but rather is used to show that every element of the claimed subject matter is disclosed by van der Ley *et al.* with the unrecited characteristics being inherent therefrom. See *In re Samour* 197 USPQ (CCPA 1978).

'To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.' *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Note that as long as there is evidence of record establishing inherency, failure of those skilled in the art to contemporaneously recognize an inherent property, function or ingredient of a prior art reference does not preclude a finding of anticipation. *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999). Also note that the critical date of extrinsic evidence showing a universal fact need **not** antedate the filing date. See MPEP 2124.

Relevant Art

12) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Walkarchuk *et al.* (*J. Biol. Chem.* 271: 19166-19173, August 1996 – Applicants' IDS) disclosed the structure of *lgtE* (*galE*) mutant of L3 immunotype of *Neisseria meningitidis* strain MC58 or H44/76, wherein a PEA moiety is linked to position 3 of HepII moiety of the inner core. See Figure 6; second full paragraph on right column on page 19172; and sentence bridging the two columns on page 19171.

♦ van der Ley *et al.* (*FEMS Microbiol. Lett.* 146: 247-253, 1997) disclosed a *galE* inactivated mutant of *Neisseria meningitidis* H44/76 and a method of inducing an antibody that binds both to wild type *Neisseria meningitidis* and *galE* mutant of *Neisseria meningitidis*. The antibody was produced by immunizing mice with *galE* mutant LPS from *galE* immunotype L3 H44/76 strain, the inner core of which LPS comprises Hep2 substituted with phosphoethanolamine. See Table 1; sections 2.1 and 2.5; Figure 4; and page 252.

♦ Gu *et al.* (*Infect. Immun.* 61: 1873-1880, 1993) taught an antigenic conjugate comprising a carrier protein covalently bonded to the conserved portion of a Gram negative bacterial lipooligosaccharide (LOS). The LOS was derived from the Gram negative bacterium, group A *Neisseria meningitidis*. The conserved region of the molecule, i.e. the KDO, was coupled to tetanus toxoid via adipic acid dihydrazide. The use, in conjugation, of tetanus toxoid carrier protein, and the use of compounds such as adipic acid dihydrazide (ADH) and 1-ethyl-3-(3-dimethylamino propyl) carbodiimide (EDAC) were taught (see page 1874). The antigenicity of such conjugates was "conserved", and the antisera raised to one of these conjugate vaccines in a rabbit "cross-reacted" with most of 12 group A meningococcal prototype lipooligosaccharides and also with lipopoligosaccharides of two pathogenic group B meningococcal strains. Gu *et al.* further taught that the antigenic "conjugates derived from A1 LOS can induce antibodies against many LOS immunotypes from different organism serogroups, including group B" (see the abstract). That a cross reactive immune response was induced by Gu's conjugate against heterologous strains of group A meningococci (i.e., group A *Neisseria meningitidis*) as well as against two pathogenic strains of a heterologous serogroup B (i.e., group B *Neisseria meningitidis*) is illustrated in Figure 3. Group A meningococcal LOS, A1, was chosen for the preparation of the antigenic conjugate because "it shares epitopes with strains carrying other LOS immunotypes". The immune response elicited by the conjugate was bactericidal not only to the homologous strain, but also to heterologous group B meningococcal strains (see page 1879).

♦ Poolman JT (*Infectious Agent and Disease* 4: 13-28, 1995) disclosed of the existence of phosphoethanolamine moiety linked to position 3 of Hep2 moiety of the inner core of the lipopolysaccharide of native and *galE* immunotype L3 of *Neisseria meningitidis*. See Figure 2.

Remarks

13) Claims 48, 49, 55, 56 and 62-81 stand rejected.

14) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number (571) 273-8300, which receives facsimile transmissions 24 hours a day and 7 days a week.

15) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

16) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

May, 2007

S. DEVI, PH.D.
PRIMARY EXAMINER